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(54) **Preparations for the treatment of dermatoses.**

(57) An external preparation for the treatment of dermatoses is in the form of an ungelled ointment or cream comprising indomethacin as an active component and preferably also containing an adjuvant for increasing the release of indomethacin from the preparation. Such preparations exhibit a superior remedial effect when applied directly to any affected parts of the skin.

EP 0 055 029 A2

"PREPARATIONS FOR THE TREATMENT OF DERMATOSES"

The present invention relates to preparations for the treatment of dermatoses, and more particularly to external preparations (i.e. preparations intended for external application) for the treatment of dermatoses which comprise indomethacin as an active component.

At present, indomethacin is being widely used as a non-steroidal anti-inflammatory agent. However, medication with indomethacin induces adverse effects such as gastoenteric disorders in the form of stomach-ache and vomitting, due primarily to oral administration. This has given an impetus to the development of medicaments in which indomethacin is applicable in the form of a suppository, a combined drug, or a prolonged action drug.

A gelled ointment containing indomethacin has recently been developed for the treatment of rheumatism, arthritis, osteoarthritis, scaplulohumeral peri-arthritis, myalgia and like conditions in the field of orthopedic surgery.

Indomethacin exhibits an outstanding remedial effect on dermatoses, but a gelled ointment prepared from indomethacin is irritating when applied directly to injured skin. The topical application of indomethacin is practically impossible, and thus, indomethacin must be administered through an oral route or in the form of a suppository. The medication of indomethacin in such a form, however, involves the above-mentioned side effects and requires larger dosages so as to be rendered actually effective than does the external use. There has thus been a demand for the development of an external preparation for the treatment of dermatoses that can be applied directly to any affected parts of the skin. Such preparation has not hitherto been realized because indomethacin is neither retained well on the skin nor

absorbed well by the skin and is likely to cause ulcers on injured skin.

In order to overcome the foregoing disadvantages of the existing techniques, the present inventors have carried out a series of researches leading to the development of external preparations of indomethacin for the treatment of dermatoses which can be applied directly to any affected skin parts.

Because of the insolubility in water and common solvent, indomethacin merely suspends in a base when prepared into an ointment or cream, and the suspended component is not well absorbed by the skin and consequently does not exhibit any great remedial effect. As a result of further studies to solve this problem, the present inventors have found that it is possible to improve the properties of indomethacin as far as its retention on and absorption by the skin are concerned, and to improve its remedial effect, if a specific adjuvant is added to increase the release of indomethacin from the preparation.

It is accordingly an object of the present invention to provide an external preparation for the treatment of dermatoses which contains indomethacin and which is completely devoid of the disadvantages of the previously used techniques, and which can be applied directly to an affected skin part.

According to the invention, there is provided an external preparation in the form of an ungelled ointment or cream for the treatment of dermatoses, comprising an effective amount of indomethacin as an active component.

The external preparations for the treatment of dermatoses according to the invention can be prepared by incorporating indomethacin with agitation into an externally useful common base, preferably together with an adjuvant for increasing the release of indomethacin.

Suitable bases for external use in the invention include those bases which do not irritate even injured parts of the skin and are employed generally for the preparation of ointments and creams.

Suitable adjuvants for increasing the release of indomethacin include those substances which can readily solubilize indomethacin and are miscible with a variety of bases. Examples of such adjuvants are monohydric alcohols such as ethanol, isopropanol and benzyl alcohol; polyhydric alcohols such as propylene glycol, butylene glycol, glycerine and polyethylene glycol; fatty acid esters such as diisopropyl adipate, isopropyl palmitate, lauryl lactate and decyl oleate; surface-active agents such as polyoxyethylene sorbitan monooleate, polyoxyethylene hardened castor oil derivatives and polyoxyethylene higher alcohol ethers; essential oils such as menthol, camphor and methyl salicylate; and crotamiton.

The external preparations for the treatment of dermatoses, according to the invention, preferably contain 0.1 to 7% by weight, more preferably 0.5 to 5.0% by weight of indomethacin as an active component and preferably also 0.1 to 50% by weight of an adjuvant for increasing the release of indomethacin. Such external preparation may additionally contain antioxidants, surface active agents, antiseptics and pH-adjusting agents.

The external preparations according to the invention are particularly effective for the treatment of contact-type dermatitis, atopic dermatitis, psoriasis vulgaris, acute and chronic eczema, zoster, decubitus, solar dermatitis, radio-ulcers, burn ulcers and similar conditions.

In addition, the external preparations of the invention are stable in storage over a long period of time and are not irritating to the skin, and can thus be applied directly to any affected parts of the skin.

As compared with conventional oral administration or suppository medication, the topical application of indomethacin as contemplated by the invention exhibits a superior anti-inflammatory analgesic action with a very small quantity of the active component.

The invention will now be further described with reference to the following experimental examples and inventive examples which are provided for purposes of illustration only and are not intended to be limiting unless otherwise specified.

Reference will also be made to the drawing which is a graph showing the relationship between the amount of indomethacin released and time for preparations according to certain of the inventive examples and for a control preparation.

Experimental Example 1

Inhibitory effect on carrageenan-induced edema:

Wistar male rats each weighing about 200 g, arranged in groups each consisting of twelve animals, were given subcutaneously 0.05 mℓ of a 1% carrageenan solution on their hind right paws. Immediately thereafter, about 100 mg of an ointment prepared as in Example 1 below, was coated onto each injected region which was covered with a commercially available plastic film [Kure-Wrap (Trade Mark) made by Kureha Chemical Co., Ltd.] and held thereon by means of gauze. Two hours later, the film and gauze were removed. One hour after such removal, the weight of edema was measured. A control group of animals was coated only with an ointment base and thereafter treated in the same manner as in the subject test groups.

The results obtained are as shown in Table 1 :-

Table 1

Agent	Weight of edema (g) Mean ± error	Inhibition ratio (%)
Control	0.73 ± 0.04	-
Indomethacin ointment (1%)	0.57 ± 0.03	21.9*

* $p < 0.01$

Experimental Example 2

Inhibitory effect on acceleration of blood vessel permeability:

Guinea pigs arranged in groups each consisting of six animals were coated twice with about 50 mg of the ointment prepared as in Example 1 below, on the skin of their backs after the hair had been removed, at an interval of one hour. One hour after the second coating, a 1% Evans Blue solution was injected intravenously, and 10 µg of a histamine hydrochloride solution was immediately injected intradermally into each ointment-coated region. 30 minutes later, the animals were decapitated and exsanguinated. Each blue-dyed skin was exfoliated, and the pigment was extracted with pyridine and determined. A control group of animals was coated only with an ointment base and thereafter treated in the same manner as in the subject test groups.

The results obtained are as shown in Table 2.

Table 2

Agent	Evans Blue (µg/region) Mean ± error	Inhibition ratio (%)
Control	49.2 ± 5.3	-

Indomethacin ointment (1%)	33.1 ± 4.9	32.7**

** $p < 0.05$

Experimental Example 3

Release from various bases:

Ointments prepared respectively as in Examples 3 to 8 below, each weighing 2 g, were shaken at 25°C in a cellulose tube dipped in 30 mℓ of a phosphate buffer solution (pH 7.0). After an interval of 1, 3, 5 and 10 hours, sampling was made to determine the quantities of indomethacin dissolved. For purposes of control, the steps noted above were carried out for an ointment of the same recipe as in Example 8, except that no adjuvant was added for increasing the release of indomethacin.

The results obtained are shown in the accompanying drawing in which curve 1 represents the ointment prepared as in Example 3; curve 2, Example 4; curve 3, Example 5; curve 4, Example 6; curve 5, Example 7; curve 6, Example 8; and curve 7, the control.

Example 1

Materials :

1)	Indomethacin	1.0% by weight
2)	White Vaseline (Trade Mark)	15.0% " "
3)	Liquid paraffin	6.0% " "
4)	Cetanol	3.0% " "
5)	Stearyl alcohol	3.0% " "
6)	Polyoxyethylene cetyl ether	2.5% " "
7)	Propylene glycol	5.0% " "
8)	Purified water	An amount sufficient to bring the final weight to 100%

Method:

A) Heat and melt 1) to 7).

B) Add heated 8) to the mixture of 1) to 7).

C) Stir the resulting mixture until it has cooled to room temperature and becomes a semi-solid preparation.

Example 2

Materials :

1)	Indomethacin	3.0% by weight
2)	Benzyl alcohol	10.0% " "
3)	Sorbitan sesquioleate	1.5% " "
4)	Liquid paraffin	12.0% " "
5)	Solid paraffin	6.0% " "
6)	White Vaseline (Trade Mark)	67.5% " "

Method :

A) Heat and melt 3) to 6).

B) Disperse 1) in 2) with heating, and add this solution to the mixture of 3) to 6).

C) Stir the resulting mixture until it has cooled to room temperature and becomes a semi-solid preparation.

Example 3

In this Example and Examples 4 to 9 below, the preparations were produced in the same manner as in Example 1 or Example 2, as appropriate.

1)	Indomethacin	0.5% by weight
2)	White Vaseline (Trade Mark)	15.0% " "
3)	Liquid paraffin	6.0% " "
4)	Cetanol	3.0% " "
5)	Stearyl alcohol	3.0% " "
6)	Polyoxyethylene cetyl ether	2.5% " "
7)	Propylene glycol	5.0% " "
8)	Purified water	An amount sufficient to bring the final weight to 100%

Example 4

1)	Indomethacin	0.5% by weight
2)	Propylene glycol	15.0% " "
3)	Sorbitan sesquioleate	1.0% " "
4)	Liquid paraffin	10.0% " "
5)	Solid paraffin	5.0% " "
6)	White Vaseline (Trade Mark)	68.5% " "

Example 5

1)	Indomethacin	0.5% by weight
2)	White Vaseline (Trade Mark)	15.0% " "
3)	Liquid paraffin	6.0% " "
4)	Cetanol	3.0% " "
5)	Stearyl alcohol	3.0% " "
6)	Polyoxyethylene cetyl ether	2.5% " "
7)	Crotamiton	5.0% " "
8)	Purified water	An amount sufficient to bring the final weight to 100%

Example 6

1)	Indomethacin	0.5% by weight
2)	Benzyl alcohol	8.0% " "
3)	Sorbitan sesquioleate	1.0% " "
4)	Liquid paraffin	10.0% " "
5)	Solid paraffin	5.0% " "
6)	White Vaseline (Trade Mark)	75.5% " "

Example 7

1)	Indomethacin	0.5% by weight
2)	Polyoxyethylene sorbitan monooleate	20.0% " "
3)	Liquid paraffin	10.0% " "
4)	Solid paraffin	5.0% " "
5)	White Vaseline (Trade Mark)	64.5% " "

Example 8

1)	Indomethacin	0.5% by weight
2)	Diisopropyl adipate	10.0% " "
3)	Liquid paraffin	10.0% " "
4)	Solid paraffin	5.0% " "

5)	White Vaseline (Trade Mark)	74.5% " "

Example 9

1)	Indomethacin	1.0% by weight
2)	Stearyl monoglyceride	10.0% " "
3)	Stearic acid	2.0% " "
4)	Polyoxypropylene cetyl ether	3.0% " "
5)	Isopropyl myristate	20.0% " "
6)	Diethyl sebacate	5.0% " "
7)	Polyethylene glycol	10.0% " "
8)	Paraoxymethyl benzoate + paraoxypropyl benzoate	0.2% " "
9)	Purified water	An amount sufficient to bring the final weight to 100%

Example 10

Clinical studies on the remedial effect of the external preparations according to the present invention were conducted in three selected medical institutions. In these studies, the ointment produced in Example 9 was used and evaluated by application to 60 patients suffering from dermatoses.

The results obtained are as shown in Tables 3 and 4.

The results obtained are as shown in Tables 3 and 4.

Table 3. Efficacy by Dermatoses

Dermatosis	Degree of efficacy *)				Number of dermatoses
	A	B	C	D	
Herpes zoster	5	18	5	1	29
Herpes simplex	1	2	1	0	4
Eczema and dermatites	2	0	0	1	3
Erythemas	4	7	8	0	19
Scalding	1	0	1	0	2
Chilblain	2	1	0	0	3
Total	15 (25.0%)	28 (46.7%)	15 (25.0%)	2 (3.3%)	60 (100%)

Table 4. Efficacy by Symptoms

Symptom	Degree of efficacy *)				Number of symptoms
	A	B	C	D	
Pain	15	17	0	1	33
Erythema	12	16	4	1	33
Swelling	10	7	10	3	30
Total	37 (38.5%)	40 (41.7%)	14 (14.6%)	5 (5.2%)	96 **) (100%)

*) The degree of efficacy is expressed as follows:

A: Excellent C: Good

B: Fair D: Bad or ineffective

**) Because some of the patients had more than one symptom, the total number of symptoms is greater than that of the dermatoses.

CLAIMS

1. An external preparation in the form of an ungelled ointment or cream for the treatment of dermatoses, comprising an effective amount of indomethacin as an active component.

2. A preparation as claimed in Claim 1, characterised in that said indomethacin is present in an amount of 0.1 to 7% by weight of the preparation.

3. A preparation as claimed in Claim 2, characterised in that said indomethacin is present in an amount of from 0.5 to 5.0% by weight of the preparation.

4. A preparation as claimed in any one of Claims 1 to 3, which further includes an adjuvant for increasing release of said indomethacin in use, said adjuvant being selected from monohydric alcohols, polyhydric alcohols, fatty acid esters, surface-active agents, essential oils and crotamiton, or mixtures of two or more thereof.

5. A preparation as claimed in Claim 4, characterised in that said adjuvant is present in an amount of from 0.1 to 50% by weight of the preparation.

6. A preparation as claimed in any one of Claims 1 to 5 for use in the treatment of one of the dermatoses, dermatitis, eczema, psoriasis, zoster, ulcerative dermatitis and decubitus.